

# Effect of HIV-1 infection and increasing immunosuppression on menstrual function

Oliver C. Ezechi<sup>1</sup>, Andrea Jogo<sup>2</sup>, Chidinma Gab-Okafor<sup>1</sup>, Dan I. Onwujekwe<sup>3</sup>, Paschal M. Ezeobi<sup>3</sup>, Titi Gbajabiamila<sup>3</sup>, Rosemary A. Adu<sup>3</sup>, Rosemary A. Audu<sup>4</sup>, Adesola Z. Musa<sup>3</sup>, Olumuyiwa B. Salu<sup>4</sup>, Emily Meschack<sup>4</sup>, Ebiere Herbertson<sup>3</sup>, Nkiru Odunukwe<sup>3</sup> and Oni E. Idigbe<sup>3</sup>

<sup>1</sup>Sexual and Reproductive Health Research Unit, <sup>3</sup>HIV & TB Research Unit, Clinical Sciences Division, <sup>4</sup>Human Virology Laboratory, Microbiology Division, Nigerian Institute of Medical Research, Lagos, and <sup>2</sup>Department of Obstetrics and Gynaecology, Federal Medical Centre, Markurdi, Nigeria

## Abstract

**Aim:** The aim of this study was to determine the prevalence, pattern and determinants of menstrual abnormalities in HIV-positive Nigerian women.

**Methods:** A cross-sectional study was carried out involving 3473 (2549 HIV-seropositive and 924 seronegative) consecutive and consenting women seen at the HIV treatment centers at the Nigerian Institute of Medical Research, Lagos and the Federal Medical Centre, Markurdi.

**Results:** The sociodemographic characteristics of the two groups were comparable, except for body mass index (BMI): the HIV-negative women ( $28.1 \pm 8.1$ ) had statistically significantly ( $P < 0.005$ ) higher BMI compared to the HIV-positive women ( $21.9 \pm 7.5$ ). Menstrual abnormalities were significantly more common in women living with HIV/AIDS (29.1%) compared to the HIV-negative (18.9%) women ( $P < 0.001$ ). The proportions of women in the two groups with intermenstrual bleeding, menorrhagia, hypermenorrhea, and post-coital bleeding were similar ( $P > 0.005$ ), however amenorrhea, oligomenorrhea, irregular periods and secondary dysmenorrhea were more common in the HIV-positive women ( $P < 0.02$ ). Primary dysmenorrhea was less common in HIV-positive women ( $P < 0.03$ ). Among the HIV-positive women, menstrual dysfunction was more common in women living with HIV/AIDS with opportunistic infections, CD4 count  $< 200$ , not undertaking therapy, symptomatic disease and BMI  $< 20$ . However, after controlling for cofounders, only CD4  $< 200$  (odds ratio [OR], 3.65; 95% confidence interval [CI], 1.2–9.7), BMI  $< 20$  (OR, 2.4; 95%CI, 1.3–3.5) and not taking antiretroviral drugs (OR, 2.05; CI, 1.7–6.5) were associated with amenorrhea, oligomenorrhea, irregular periods and secondary dysmenorrhea.

**Conclusion:** HIV-positive women in this study experienced more menstrual abnormalities of amenorrhea, oligomenorrhea, and irregular periods compared to the HIV-negative controls. HIV-positive women with CD4 count  $< 200$ , BMI  $< 20$  and who do not take antiretroviral drugs are at the greatest risk.

**Key words:** antiretroviral drug, HIV/AIDS, immunosuppression, menstrual abnormality.

## Introduction

Infection with HIV results in a chronic systemic illness with multi-organ involvement, severe immunosuppression and profound cachexia. Several other chronic

diseases that do not affect the reproductive tract directly have been shown to be associated with menstrual dysfunction.<sup>1</sup> Thus there is a theoretical possibility that HIV infection, being a systemic and chronic disease, has an adverse effect on menstrual function.<sup>1–3</sup>

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Reprint request to: Dr Oliver C. Ezechi, P.O. Box 488, Surulere, Lagos, 231lag Nigeria. Email: oezechi@yahoo.co.uk

While weight loss and changes in nutritional status may underlie these effects,<sup>3,4</sup> it may also be due to alterations in hormone metabolism secondary to either stress associated with chronic diseases, or direct effect on the reproductive organs and endocrine organs.<sup>1</sup> Although women with HIV infection often consult their health-care providers about changes in their menstrual cycles, the observation of menstrual abnormality in women with both early and advanced disease makes it uncertain as to whether HIV infection, *per se*, affects menstrual function.<sup>1</sup>

While earlier reports suggested that HIV-seropositive women may have an increased prevalence of menstrual disturbances,<sup>5,6</sup> subsequent studies yielded contradictory results. While four studies reported an association,<sup>2,7-9</sup> two others reported no association<sup>10,11</sup> between oligomenorrhea, amenorrhea, menorrhagia or dysmenorrhea and HIV serostatus or CD4+ lymphocyte counts. The fact that many women diagnosed with HIV/AIDS are within the reproductive age group and may suffer from other systemic illnesses, weight loss, and substance abuse that may have an impact on menstrual function indicates that the effect of HIV infection may not be easily delineated.<sup>1,2,4</sup>

A properly designed study is therefore necessary to distill the effect of HIV infection and immunosuppression on menstrual function, especially when most of the previous studies have not permitted an assessment of the relative contribution of HIV infection, disease stage, degree of immunosuppression, substance abuse, socioeconomic status or the use of antiretroviral drugs to menstrual abnormalities.

This study was conducted in order to determine the prevalence, pattern and determinants of menstrual abnormalities in HIV-positive Nigerian women.

## Methods

All consecutive, eligible and consenting women aged 18–40 years seen at the HIV counseling and testing centers and HIV care, treatment and support centers of the Nigerian Institute of Medical Research (NIMR), Lagos and the Federal Medical Centre (FMC), Markurdi, Nigeria during the period July 2005 to August 2007 were studied. Ethical approval was obtained from both institutions. All of the women were interviewed for their menstrual pattern in the last 6 months using a questionnaire designed for the study. Information also obtained included sociodemographic characteristics, anthropometric measurements, CD4

and viral load values. The details of their last normal menstrual period, duration and severity of bleeding and dysmenorrhea, the occurrence of dyspareunia, and the length of the menstrual cycle were recorded. Regular cycles were defined as occurring at a 21–35 day interval. Oligomenorrhea was defined as a menstrual cycle lasting 36 to 90 days and amenorrhea as lack of menses for more than 90 days.

Excluded from the study were non-consenting women, women using hormonal contraception in the last 6 months, women on intrauterine contraceptive devices, women with palpable uterine fibroid, pregnant women, recently delivered women and breastfeeding women. Also excluded were women with other chronic medical disorders.

Verbal consent was obtained before the interview after full explanation of the nature of the study.

The HIV serostatus of the subjects was determined using the recommended Nigerian National guideline algorithm of positive double enzyme linked immunosorbent (ELISA) assay. In addition, all double-ELISA-positive cases seen at the Nigerian Institute of Medical Research were confirmed with Western blot confirmatory assay and had CD4 count and viral loads determined at the Human Virology Laboratory of the institute. The patients seen at the FMC in Markurdi were not used for the CD4 count and viral load analysis because it was either not available or it was unable to be extracted from their records.

Data entry and analysis was with SPSS for Windows version 10.

## Results

A total of 3473 (2549 HIV-seropositive and 924 seronegative) consecutive and consenting women seen either for HIV testing, initial HIV clinic visit, monthly antiretroviral (ARV) drug pick-up or consultation visits during the period were eligible for the study. While 3224 of the total recruited subjects were seen at NIMR, the remaining 249 were seen at FMC. A total of 498 women were also seen during the same period but were excluded from the study because they were aged below 18 years or above 40 years (91), they were on hormonal contraception or on an intrauterine contraceptive device (13), had uterine fibroid (seven), refused consent to participate (55), were pregnant (229) or had recently delivered an infant and/or were breastfeeding (103). The CD4 count and viral load of the 147 HIV-positive women seen at the FMC were not avail-

able and thus their data were not used for the analysis of the association between CD4 and viral load with menstrual functions.

The sociodemographic characteristics of the women in the two groups studied are shown in Table 1.<sup>12</sup> The characteristics are comparable in all the parameters compared, except in body mass index (BMI) in which the HIV-negative women ( $28.1 \pm 8.1$ ) had statistically significantly ( $P < 0.005$ ) higher BMI compared with the HIV-positive women ( $21.9 \pm 7.5$ ).

The menstrual irregularities reported by the respondents in both groups are shown in Table 2. A total of 742 (29.1%) of the 2549 HIV-positive women reported menstrual irregularities compared to 175 (18.9%) of the 924 HIV-negative women. The difference was statistically significant ( $P < 0.001$ ). The proportions of women in the two groups with intermenstrual bleeding, menorrhagia and dysmenorrhea were similar. However amenorrhea, oligomenorrhea, irregular periods and postcoital bleeding were more common in the HIV-positive women (See Table 2).

Table 3 shows the correlations between the sociodemographic characteristics of the HIV-positive women

with and without menstrual symptoms.<sup>12</sup> There is a statistically significant preponderance of women with opportunistic infections ( $P < 0.001$ ), CD4 counts less than 200 ( $P < 0.001$ ), viral load of 10 000 and above ( $P < 0.001$ ), non-use of ARV drugs ( $P < 0.016$ ) and BMI less than 20 ( $P < 0.01$ ) among the women with menstrual symptoms compared with the women without menstrual symptoms. There were no significant differences in the number of women with respect to age ( $P = 0.95$ ), parity ( $P = 0.62$ ) or socioeconomic status ( $P = 0.92$ ). However, after controlling for the potential confounding variables (Table 4) only CD4  $< 200$  (odds ratio [OR], 3.56; 95% confidence interval [CI], 1.2–9.7), BMI  $< 20$  (OR, 2.4; 95%CI, 1.3–3.5) and being ARV-drug-naïve (OR, 2.05; 95%CI, 1.7–6.5) were associated with menstrual abnormalities of amenorrhea, oligomenorrhea, and irregular periods.

## Discussion

Questionnaire-based assessment of menstrual regularity is at best an approximation of female reproductive status because regular cycles of 21–35 days may in fact

**Table 1** The sociodemographic and biological characteristics of the HIV-positive and -negative women studied

Characteristics	HIV status of the women studied		P-value
	HIV-positive ( <i>n</i> = 2549)	HIV-negative ( <i>n</i> = 924)	
Mean age (years)	32.7 ± 4.9	33.2 ± 5.7	0.139
Mean parity	1.6 ± 0.7	1.6 ± 1.0	0.621
Mean body mass index	21.9 ± 7.5	28.1 ± 8.1	<0.005
Social class			
• I&II (Upper classes)	278 (10.9%)	96 (10.4%)	0.785
• III (Middle classes)	530 (20.8%)	201 (21.8%)	
• IV & V (Lower classes)	1741 (68.3%)	627 (67.8%)	
Educational level completed			
□ None	245 (9.6)	93 (10.1)	0.61
□ Primary	579 (22.7)	203 (21.9)	
□ Secondary	1218 (47.8)	427 (46.2)	
□ Tertiary	507 (19.9)	201 (21.8)	

**Table 2** Pattern of menstrual symptomatology among the women studied

Menstrual symptoms	HIV status of the women studied		P-value
	HIV-positive ( <i>n</i> = 2549)	HIV-negative ( <i>n</i> = 924)	
Women with menstrual irregularities	742 (29.1%)	175 (18.9%)	0.0000
• Irregular periods	201 (7.9)	40 (4.4)	0.0004
• Oligomenorrhea	163 (6.4)	36 (3.9)	0.007
• Amenorrhea	97 (3.8%)	17 (1.8%)	0.006
• Postcoital bleeding	75 (2.9%)	12 (1.3%)	0.009
• Intermenstrual bleeding	103 (4.0%)	33 (3.6%)	0.59
• Menorrhagia	37 (1.5)	19 (2.1)	0.27
• Dysmenorrhea	66 (2.6)	18 (1.9)	0.034

**Table 3** Relationship between sociodemographic characteristics of the HIV-positive women studied and menstrual symptoms

Characteristics	Women with menstrual abnormalities ( <i>n</i> = 742)	Women without menstrual abnormalities ( <i>n</i> = 1807)	<i>P</i> -value
Age			
<24	286 (38.5%)	674 (37.3%)	0.65
25–34	351 (47.3%)	891 (49.3%)	
≥35	105 (14.2%)	242 (13.4%)	
Parity			
P0	204 (27.5%)	459 (25.4%)	0.40
P1–4	485 (65.4%)	1198 (66.3%)	
≥P5	53 (7.1%)	150 (8.30%)	
Socioeconomic class			
I&II (Upper classes)	94 (12.7%)	222 (12.3%)	0.86
III (Middle classes)	157 (21.2%)	399 (22.1%)	
IV & V (Lower classes)	491 (66.1%)	1186 (65.6%)	
Mean body mass index			
<20	237 (31.0%)	390 (21.6%)	0.000
20–24	391 (52.7%)	976 (54.0%)	
≥25	114 (15.4%)	441 (24.4%)	
CD4 cell count†			
200	409 (60.0%)	143 (8.3%)	0.000
200–499	130 (19.1%)	495 (28.8%)	
≥500	143 (20.9%)	1082 (62.9%)	
Viral load†			
<1000	128 (18.8%)	808 (47.0%)	0.000
1000–9999	190 (27.9%)	441 (25.6%)	
≥10 000	364 (53.7%)	471 (27.4%)	
Presence of opportunistic infections	281 (37.9%)	374 (20.7%)	0.000
Not on antiretroviral therapy	369 (49.7%)	351 (19.4%)	0.016

†For CD4 count and viral load analysis only 2402 patients with results were used for this analysis.

**Table 4** The results of factors found to be independently associated with menstrual irregularities after controlling for potential confounding variables

Factors independently associated with menstrual irregularity	Odds ratio	95% confidence interval
CD4 count less than 200	3.56	1.2–9.7
Body mass index less 19.5	2.4	1.3–3.5
Antiretroviral-drug-naïve	2.05	1.7–6.5

be anovulatory or masked luteal phase inadequacies that may be detected only by direct hormone concentration measurement.<sup>13</sup> In this study, participants identified their menses as regular, irregular or absent for more than 5 weeks. If the menses was absent for more than 5 weeks, the women further classified it as either absent for less than 3 months or absent for more than 3 months. We are also mindful of the fact that problems can occur

with the use of recall menstrual histories. The similar sociodemographic profile of the subjects in both arms (see Table 1) hopefully will have obliterated, or reduced to the minimum, the effect of problems associated with the use of menstrual recall on the final result.

The 29.1% prevalence of abnormalities of menstrual function in the HIV-positive women reported in this study is higher than that reported by previous studies

that found increased prevalence of menstrual abnormalities in people living with HIV/AIDS (PLWHA). This difference may be due to the fact that most of the previous studies were conducted in developed countries,<sup>2,7-9</sup> where a significant number of patients present during the asymptomatic stage of HIV infection, in contrast with developing countries like ours where most patients present during the symptomatic stage of HIV infection.<sup>13</sup> Also, HIV infection occurs disproportionately among women who are poor, of minority racial or ethnic backgrounds, and who use illicit drugs. A variety of medical problems may occur in such persons, regardless of whether HIV infection is present or absent. Conditions that have been underappreciated in such populations may first come to attention when HIV infection occurs, either because infection increases the frequency or manifestations of co-morbid conditions, or because greater attention is paid to them when they are recognized in the context of HIV infection.<sup>2,14,15</sup>

In this study, in order to remove the possible effect of such factors, women of similar sociodemographic characteristics and risk factors for HIV were deliberately chosen as control subjects (Table 1). The prevalence of menstrual irregularities among the HIV-negative controls of 18.9% in this study, though similar to the reported incidence of 18.0% in similar populations,<sup>2,16</sup> was significantly less than the 29.1% reported in this study for HIV-positive women. This confirms the findings of others<sup>2,7-9</sup> that HIV infection has an effect on menstrual function. However, some other reports contradict such an association.<sup>14,15,17</sup> These contradictory reports may be a result of the small sample size or due to the use of non-representative controls.<sup>16</sup> In this study we not only used a larger sample size but a representative control from HIV counseling and testing clinics. The finding of increased prevalence of menstrual irregularities in HIV-positive women is not surprising in that HIV infection is associated with stress and weight loss, which are proven causes of menstrual irregularity.<sup>4,11</sup> HIV infection has been shown to have a direct effect on the ovary leading to chronic anovulation, which is also associated with menstrual irregularity.<sup>4,6-8</sup> Unlike the direct or associated pathological effects of HIV infection on the ovaries, the abnormalities in the menstrual cycle and reproductive function have been better characterized in the last decade. Increased rates of oligomenorrhea and amenorrhea have been reported in HIV-infected women without AIDS-defining illnesses,<sup>18,19</sup> as well as in women with the AIDS wasting syndrome compared with those women with AIDS who have

stable weight or manifest only mild weight loss.<sup>18,19</sup> These latter findings are not unexpected for women with a severe catabolic illness complicating their HIV infection.<sup>19</sup>

The proportions of women in the two groups with intermenstrual bleeding, menorrhagia and dysmenorrhea were similar. However amenorrhea, oligomenorrhea and irregular periods were more common in the HIV-positive women (See Table 2). From the above finding it seems safe to assume that the effect of HIV infection on menstrual function is related to anovulation as symptoms of amenorrhea, oligomenorrhea and irregular periods are major symptoms of chronic anovulation.<sup>1,4,7</sup> The findings of intermenstrual bleeding, menorrhagia and dysmenorrhea have not been significantly associated with HIV infection, which confirms reports of earlier findings linking menstrual irregularity in women with HIV to the direct effect of HIV on the ovaries.<sup>20,21</sup> While menstrual symptoms of amenorrhea, oligomenorrhea and irregular period are known symptoms of anovulation, intermenstrual bleeding, menorrhagia and dysmenorrhea may result from various conditions, ranging from infections to uterine fibroids.<sup>20-22</sup>

The findings of low CD4 count (OR, 3.56; 95%CI, 1.2-9.7), BMI less than 20 (OR, 2.4; 95%CI, 1.3-3.5) and ARV-drug-naïvity (OR, 2.05; 95%CI, 1.7-6.5) as having independent association with the menstrual abnormalities of amenorrhea, oligomenorrhea, and irregular periods after controlling for potential confounders (Table 4) support the above assertions. Severe HIV diseases as indicated by a CD4 count less than 200 is associated with severe wasting. Also the use of ARV in HIV-positive patients is associated with improvement of well-being, subsequent weight gain and resolution of hitherto menstrual irregularities.

In summary, HIV-positive women in this study were more likely to experience menstrual abnormalities of amenorrhea, oligomenorrhea, and irregular periods compared to the HIV-negative control subjects. Among the HIV-positive women, women with CD4 count less than 200, BMI less than 20 and those who were ARV-drug-naïve were at greatest risk of these abnormalities.

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